## REMARKS

Claims 1-37 are pending in this application. By this Amendment, claims 1-32 are cancelled and new claims 38-43 are added. The new claims are supported throughout the specification, no new matter has been added.

Information Disclosure Statement

Applicants submit herewith an Information Disclosure Statement citing the Canadian Patent Reference, for consideration by the Examiner, which was omitted from the Information Disclosure Statement filed March 11, 2008.

Obvious-type Double Patenting Rejection

Applicants respectfully request that this rejected be held in abeyance until the claims are otherwise deemed allowable.

Enablement and Written Description Rejections

The Examiner has rejected claims 33-37 as allegedly non-enabled and lacking adequate written description with respect to the recitation of "solvate." Applicants respectfully traverse this rejection.

Applicants attach hereto three scientific articles showing that there are numerous and routine methods of detecting, isolating and characterizing solvates of pharmaceutical

compounds, including detection and isolation by infrared FT-Raman spectroscopy and production by crystallization, spray drying and/or freeze drying. Moreover, as discussed in on page 951 of the attached Byrn et al. reference, hydrates (one of the most common forms of solvates) can be produced by methods as routine as wet grinding. The attached references are:

1.) Byrn et al.; Pharmaceutical Research; Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations; Vol. 12; pps 945-954; 1995

2.) Yu et al.; Journal of Pharmaceutical Sciences; Existence of a Mannitol Hydrate during Freeze-Drying and Practical Implications; Vol. 88; pps 196-198; February 1999

3.) Otsuka et al.; Pharmaceutical Research; Physicochemical Stability of Phenobarbital Polymorphs at Various Levels of Humidity and Temperature; Vol. 10; pps 577-582; 1993

Accordingly, applicants submit that methods for making and using the claimed solvates would not require undue experimentation. Also, applicants respectfully submit that the claims do not specify any specific solvate forms and are generic to any solvate and therefore a description of specific solvate structures in the specification is not required to comply with the written description requirement.

Obviousness Rejection

The Examiner has rejected claims 33-37 as allegedly prima facie obvious over the Boger '183 patent ("Boger"). The Examiner alleges that claims 33-37 are obvious over Boger based on the rationale that compounds that differ in the placement of substitutes in a ring system are obvious. Applicant's respectfully traverse this rejection.

First applicants submit data below (at the end of this Response) showing that compounds falling within claims 33-37 are potent inhibitors of Raf kinase and VEGFR2 kinase.

Second applicants respectfully submit that the legal standard for chemical obviousness does not support the Examiner's rejection. Applicants direct the Examiner to Takeda Chemical Industries v. Alphapharm Pty., 492 F.3d 1350 (Fed. Cir. 2007). In the Takeda decision, the Federal Circuit specifically held that a claim to a 5-pyridyl ring ethyl was not obvious over a prior art compound having the same structure except for a change in the substituent from ethyl to methyl and a change in the location on the pyridyl ring from the number 5 atom to the number 6 atom. Moreover, in the Takeda decision, the prior art compound had the same stated properties as the claimed compound, namely anti-diabetic properties.

In the Takeda decision, the court specifically held that in order to show a prima facie case of chemical structural obviousness, the prior art must "have suggested making the

specific molecular modifications necessary to achieve the claimed invention." Id. at 1356. Furthermore, the Takeda decision held that the technique of "ring walking" necessary to derive the claimed 5-pyridyl ring compound from the prior art 6-pyridyl ring compound was not obvious to try (*id.* at 1359). In this regard, the court held that "[a]s for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes." *Id.* at. 1361. Moreover, the court held that the skilled artisan would not have selected the prior art compound as a lead compound to be modified in view of, inter alia, the fact that the prior art patent disclosed numerous compounds and the specific compound cited in the prior art was one of fifty four specifically identified compounds. Id. at 1357.

Applicants respectfully submit that the law set forth in the Takeda decision governs this rejection and that the rejection fails to comply with the standards set forth in the Takeda decision. Applicants respectfully submit that the rejection fails to set forth (1) a suggestion in the prior art to make the modification from the prior art compounds to the claimed compounds, (2) that skilled artisan would have a reasonable expectation of success in making the modification from the prior art compounds to the claimed compounds and (3) that the skilled artisan would have selected the prior art compounds cited by the Examiner as lead compounds to be modified. In particular, with respect to (3), applicants submit that the Boger patent is directed to pesticides (stated to have properties resulting in insect mortality) and therefore the skilled artisan would have viewed this reference as teaching away from modifying the Boger compounds to

achieve a human pharmaceutical compound. Furthermore, applicants submit that analogous to the facts of the Takeda decision, Boger discloses genuses comprising thousands of compounds and the compounds selected by the Examiner are among 72 compounds specified in Boger.

Accordingly, applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection. Moreover, if the Examiner maintains the rejection, applicants respectfully request that the rejection be supplemented to address items (1)-(3) as required by the Takeda decision.

**Data showing Raf kinase and VEGFR2 kinase inhibition**

Claims are further patentable over Boger because Boger teaches away from a pharmaceutical composition

**Properties of claimed compounds**

Moreover, applicants submit that the newly added pharmaceutical composition

**Receptor Inhibition Assays**

The assays were performed according to the methods described below or in slight modifications thereof:

**VEGFR2 Tyrosin-Kinase Assay**

The VEGFR2 kinase assay is performed in 384-well Streptavidine-coated FlashPlates after reconstitution of Streptavidin by pre-incubation with assay buffer for 10 minutes.

After discarding this reconstitution buffer, 5 µl of prediluted compounds, standard and control reagents, respectively, in assay buffer (50 mM Hepes/NaOH, pH7.5, 3 mM

$MgCl_2$, 3 mM $MnCl_2$, 3 µM $Na_3VO_4$, 1 mM Dithiothreithol) are pipetted into the wells followed by addition of 25 µl of the enzyme / substrate mix (3.81 ng/well VEGFR2 and 50 ng/well biotinylated poly-Glu-Tyr (4:1)). Therafter the kinase reaction is started by addititon of 20 µl ATP (final concentration 1 µM) spiked with 1 µCi/ml (50 nCi/well) $^{33}$P-ATP in kinase buffer (assay buffer substituted with 0.025 % PEG20000). After a 120 minutes room temperature incubation 40 µl per well EDTA (final concentration 30 mM) are added and plates incubated for furter 30 minutes at room temperature to stop the enzyme reaction. Finally, the reaction mix is discarded and plates are wasched twice. Bound radioactivity is counted for 30 sec/well on a TopCount NXT or equivalent counter. Epigallokatechin is used as pharmacological blank and standard with final assay concentrations of 5 µM and 150 nM, respectively. Test compounds were screened at a final concentration of 5 µM; DMSO is used for untreated controls. The final DMSO concentration in the assay is 1 % in a total assay volume of 50 µl. Radioactivity was measured with a topcount. $IC_{50}$-values were calculated in RS1.

**C-Raf Kinase Assay***

The C-Raf (Raf-1) kinase assay is performed as AlphaScreen assay in white 384-well Packard Optiplates with a reaction volume of 33 µl and a total assay volume (including detection reagents) of 53 µl. 2.5 ng/well GST-C-RAF (in-house production) in 1.1-fold kinase buffer (Cell Signaling) substituted with 0.1 % Brij35 and 0.05 % BSA were pre-incubated with 3 µl of prediluted compounds (final concentration 10 µM (in 0.75% DMSO) in 33 µl reaction volume), DMSO only for controls or a proprietary kinase inhibitor as pharmacological blank for 30 minutes at room temperature. The 60-minutes

kinase reaction is started thereafter by addition of 10 µl of a mixture of ATP (final concentration 100 µM) and biotinylated GST-MEK substrate (in-house production, 50 ng/well) in 1.1-fold kinase buffer containing 0.1 % Brij35. The AlphaScreen IgG Detection Kit (Protein A, PerkinElmer) and a rabbit anti-phospho-MEK-1/2 (Ser218/Ser222) antiserum (Santa Cruz, sc-7995-R) are used for detection of substrate phosphorylation: Equal amounts of Protein A acceptor beads and Streptavidin donor beads are diluted with AlphaScreen detection buffer (25 mM Tris/HCl pH 8.0, containing 200 mM NaCl, 132.5 mM EDTA and 0.25 % BSA) and incubated with the antiserum for 2 hours at room temperature in the dark followed by overnight incubation at + 4°C. Twenty µl of this bead suspension (final assay conc. of each, donor and acceptor beads: 10 µg/ml) are added to the reaction mix and incubated protected from light for approx. 20 hours prior to detection on a multi-label reader (e.g. EnVision) capable for detection of the AlphaScreen signal (Ex. 680 nm, Em. 570 nm). $IC_{50}$-values were calculated in RS1.

**Raf-Mek-Erk Kinase Cascade Assay****

Raf-kinase is a cytoplasmatic Serine/Threonine kinase which transmits gamma-phospate residue from ATP to Serine residues of Mek, hence activating Mek, and the activated Mek in turn phosphorylates Erk. The phosphorylation of Erk can be determined using phospho specific antibodies and thus serves as a signal for the activity of the Raf-Mek-Erk Kinase Cascade. All materials used are commercially available. 96-well microtiter plates are coated overnight with a commercially available polyclonal Erk-antibody (K-23) in a dilution of 1:5000 in $Na_2CO_3$-buffer (100µl/well) and

then blocked with TBST-buffer. The compounds to be tested are dissolved in DMSO with an end concentration of 1x $10^{-6}$ M. At an inhibition of the Cascade (inhibition > 50% at a concentration of 1x $10^{-6}$ M) by the respective tested compound the respective $IC_{50}$ of that compound is determined. Double testings are performed in each case.

**Kinase reaction**

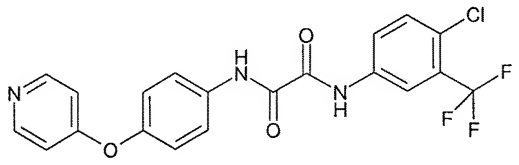
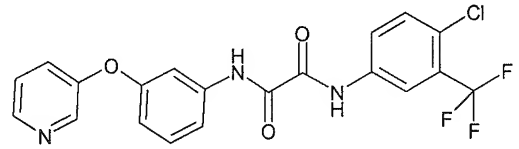
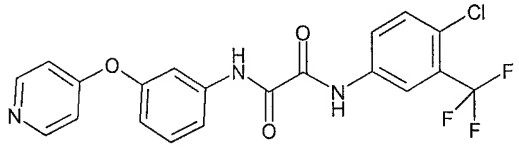
In a first batch 2.5 µl active c-Raf kinase is treated with 13.5 µl kinase buffer and 0.35 µl of a solution of the respective compound in DMSO. In a second batch 2 µl of inactive Mek1 treated with 14 µl kinase and buffer 0.35 µl of a solution of the respective compound in DMSO. In a third batch 5 µl of inactive Erk2 is treated with 10 µl kinase and buffer 0.35 µl of a solution of the respective compound in DMSO. these batches are pre-incubated for 30 min at 4°C. After the pre-incubation, 15 µl of each of the three batches is united with each other and treated with 5 µl of a ATP/$MgCl_2$-solution and mixed with a pipet. The thus obtained probes are incubatet for 30 min at 30°C (kinase reaction) in a shaking incubator (Eppendorf Thermomixer Comfort). Then, 5.6 µl of a SDS-solution (20 %) is added and the kinase reaction is stopped by incubation at 50°C for 10 min, and subsequently treated with 190 µl blocking buffer. From each of the accordingly obtained probes, 100 µl are given in a separate well of the Erk-coated 96-well microtiter plate and incubated 60 min at Roomtemperature. Then, the wells of the microtiter plate are treated with washing buffer (3x 200 µl, 5 min each).

For the detection of phosphorylated Erk, a commercially available anti-phospo-Erk antibody (p44/p42, 1:500; 100 µl in blocking buffer) is added to the wells and incubated at 4°C overnight. The wells are then treated with washing buffer (3x 200 µl, 5 min each) and incubated with HRP-conjugated IgG specific antibody (1:1000 in blocking buffer) for 60 min at room temperature. After further washing (3x 200 µl, 5 min each), the wells are treated with 100 µl/well TMB-substrate and after incubation for 2-5 min at room temperature, 1 M $H_2SO_4$ solution (100 µl/well) is added. Detection of the OD takes place at a wavelength of 450 nm with an ELISA detector (SLT 400 ATC). $IC_{50}$-values were calculated in RS1.

The data given in Table I shows that the compounds according to the invention are inhibitors of Raf kinase, and furthermore inhibitors of VEGFR2 kinase.

**Table I**

Structure, Molar Weight, HPLC Retention times and $IC_{50}$ values of test compounds in the respective assays:

| Structure | MW | $R_t$ (min) | Raf ($IC_{50}$) [mol/l] | VEGFR2 ($IC_{50}$) [mol/l] |
|---|---|---|---|---|
|  | 435.79 | 2.24 | 7,0E-06* | 7,9E-07 |
|  | 435.79 | 2.78 | 1,0E-06* | 6,0E-06 |
|  | 435.79 | 2.25 | 3,1E-07** | |

HPLC method:

Gradient: 6 min; flow rate: 1.5 ml/min from 90:10 to 0:100 $H_2O$/ACN

Water + TFA (0.1% by vol.); acetonitrile + TFA (0.1% by vol.)

Column: Chromolith SpeedROD RP 18e 50-4.6; Wavelength: 220 nm

If for any reason the Examiner feels the application is not now in condition for allowance it is respectfully requested that he contact, by telephone, the undersigned attorney at the indicated telephone number to arrange for an interview to expedite the disposition of this case.

In the event that any fees are due with respect to this paper, please charge Deposit Account No. 01-2300, referencing Atty. Docket No. 030863-00001.

Respectfully submitted,

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